Epidural analgesia improves postoperative nitrogen balance

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after epidural analgesia (during and after operation) and after general anaesthesia to evaluate the effect of neurogenic blockade.

Summary and conclusions

Postoperative nitrogen balance was monitored in twelve patients undergoing hysterectomy under either epidural analgesia or general anaesthesia. The mean cumulative five-day nitrogen losses were significantly lower after epidural analgesia than after general anaesthesia. Nitrogen sparing presumably results from inhibiting the stress-induced release of catabolic hormones, since epidural analgesia abolished postoperative hyperglycaemia and increase in plasma cortisol concentrations. No adverse effects of inhibiting the stress response were observed.

Neurogenic stimuli thus play a crucial part in the catabolic response to surgery. Inhibiting the endocrine-metabolic response to trauma by neurogenic blockade may reduce the morbidity precipitated in high-risk patients by the catabolic response to surgery.

Introduction

Surgical stress or trauma increases secretion of catabolic hormones such as cortisol,[1][2] glucagon,[3][4] and catecholamines,[5][6] but inhibits anabolic hormones such as insulin[7][8] and testosterone.[9] These endocrine changes result in mobilisation of substrate and ultimately in a catabolic state with negative nitrogen balance, which may adversely affect the postoperative course. Administering substrates,[10][11][12] insulin and glucose,[13] or growth hormone[14] improves nitrogen balance but does not diminish the release of catabolic hormones induced by stress. Neurogenic afferent stimuli from the area of trauma to the central nervous system apparently play an important part in the endocrine-metabolic response to stress.[15] This is confirmed by the effects of blocking afferent neurogenic pathways from the surgical area by epidural analgesia.[2][16-19]

In this study we compared the postoperative nitrogen balance

Patients and methods

We studied the nitrogen balance in 12 otherwise healthy premenopausal women undergoing elective abdominal hysterectomy for metrorrhagia or cancer of the cervix, stage 0-1. Their ages ranged from 27 to 49 years (mean 36 in the epidural group and 40 in the control group), and their body weight ranged from 49 to 76 kg (mean 60 and 62 kg). None of them had been taking medications or hormonal contraceptives. They were not obese and had been on a normal diet up to the day of operation. Informed consent was obtained from all subjects.

Six patients had general anaesthesia with halothane, and six epidural analgesia without general anaesthesia, induced by 0·5% bupivacaine without adrenaline (Marcain).[18] The analgesia, extending from T4 to S5, started before incision of the skin and was maintained throughout the following 24 hours, so that the patients were constantly pain free. Both groups were premedicated with pethidine, 1 mg/kg; promethazine, 12·5-25 mg; and atropine, 0·5 mg. The operations took 70-120 minutes (mean 92 minutes in both groups).

During the first 24 hours after operation all patients received only isotonic saline intravenously and tap water orally, and the following four days only oral nutrition, the intake of proteins and calories being recorded. All patients had a bladder catheter during the first day. We collected urine for five days, and determined the daily nitrogen balance from the measured intake of nitrogen and the calculated loss in the urine.

The patients did not receive blood, blood substitutes, or sympathomimetic drugs. The blood lost at operation, which never exceeded 300 ml, was replaced by 2·5 ml of isotonic saline/ml. None of the patients had postoperative complications or fever above 38°C.

Twelve blood samples (200 ml) were taken from a venous catheter—15 and 5 minutes before induction of anaesthesia or epidural analgesia, at skin incision, and ½, 1, 2, 3, 4, 6, 9, 14, and 24 hours after skin incision. They were analysed for cortisol by a competitive protein-binding technique.[20] Blood glucose and plasma urea concentrations were measured by standard automated techniques. The total nitrogen in urine was determined by measuring ammonium by the Berthelot technique after wet digestion.

Student's *t* test for paired and non-paired variables was used for significance testing.

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Results

The daily and total intake of nitrogen and energy (table) did not differ significantly between the two groups. None of the patients showed significant changes in blood urea concentrations. Comparison of the daily nitrogen balance showed no significant difference between the two groups except on the fourth day, but on each day the negative balance was greater in the control group (fig 1). The cumulative nitrogen balance (fig 2) was negative in both groups, but significantly less negative (P < 0·02) in the epidural group on the fourth and the

Daily and total intake of nitrogen and energy in 12 patients undergoing hysterectomy under epidural analgesia or general anaesthesia. Results are given as means ± SE of mean

	Days after operation:	1	2	3	4	5	Total
Nitrogen (mol)	Epidural analgesia group (n = 6) ..		0·16 ± 0·06	0·40 ± 0·09	0·45 ± 0·13	0·41 ± 0·07	1·41 ± 0·34
	General anaesthesia group (n = 6) ..		0·25 ± 0·07	0·36 ± 0·09	0·40 ± 0·06	0·43 ± 0·07	1·43 ± 0·25
Energy (MJ)	Epidural analgesia group (n = 6) ..		1·80 ± 0·54	3·15 ± 0·65	3·45 ± 0·74	3·88 ± 0·82	12·29 ± 2·61
	General anaesthesia group (n = 6) ..		1·98 ± 0·47	2·68 ± 0·88	3·64 ± 0·74	3·45 ± 0·66	11·74 ± 2·34

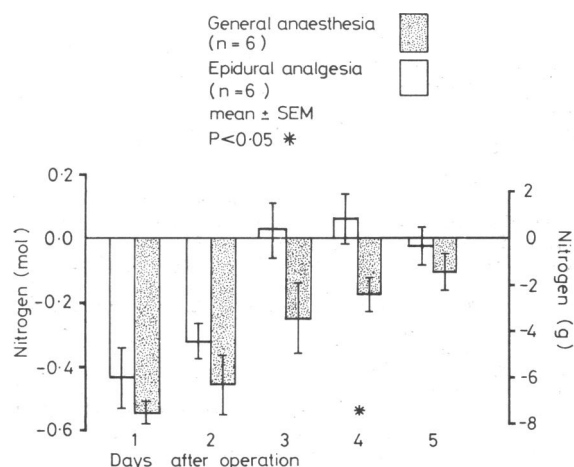*Conversion: SI to traditional units*—Nitrogen: 1 mol ≈ 14 g. Energy: 1 MJ ≈ 240 kcal.

FIG 1—Daily nitrogen balance in 12 patients undergoing hysterectomy under epidural analgesia or general anaesthesia.
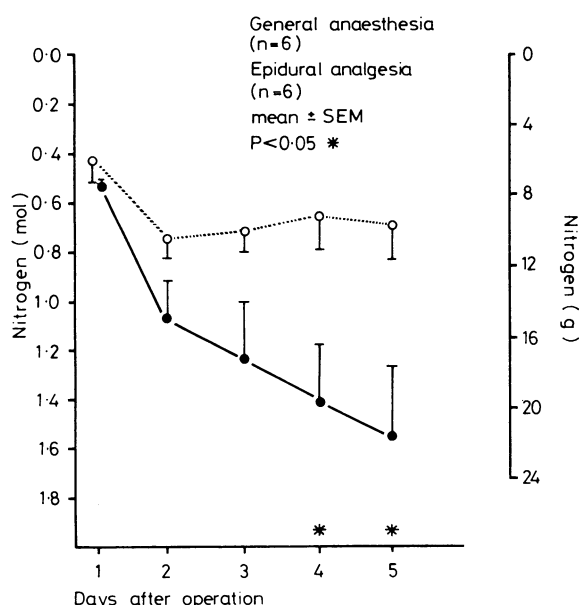

FIG 2—Cumulative nitrogen balance in 12 patients undergoing hysterectomy under epidural analgesia or general anaesthesia.
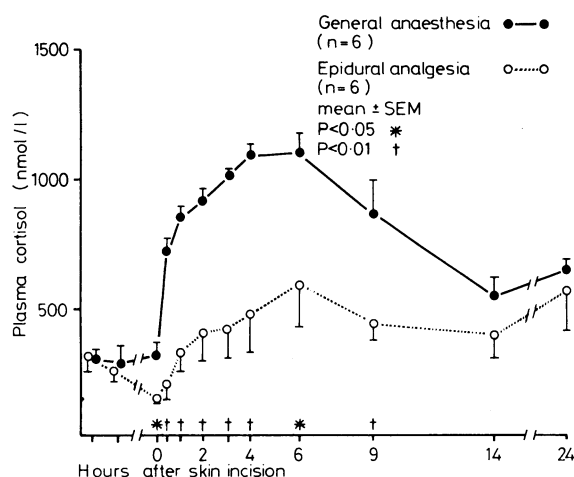

FIG 3—Plasma cortisol concentrations during and after hysterectomy under general anaesthesia and under epidural analgesia.
   Conversion: SI to traditional units—Plasma cortisol: 1nmol ≈ 36 ng/100 ml.

fifth postoperative days. By the fifth day it was $0.7 \pm SE$ of mean 0.14 mol $(10 \pm 2$ g) in the epidural group and 1.54 ± 0.28 mol $(22 \pm 4$ g) in the control group. Even on the second day after operation the patients in the epidural group were in nitrogen balance, whereas the control group showed a negative nitrogen balance throughout the study.

The concentrations of plasma cortisol (fig 3) and blood glucose (fig 4) rose significantly during and after operation in the control group, but this response did not occur in the epidural group.
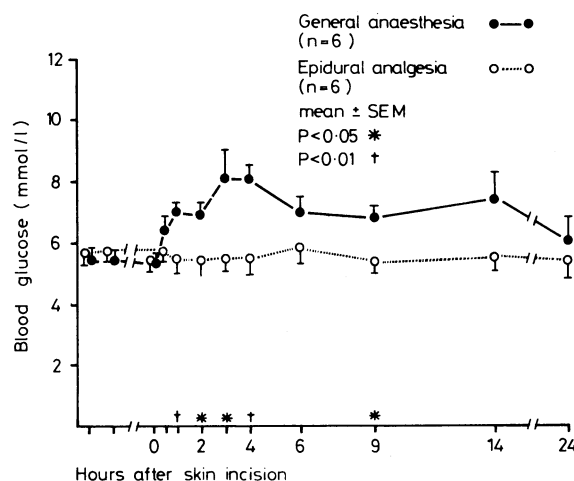

FIG 4—Blood glucose concentrations during and after hysterectomy under general anaesthesia and under epidural analgesia.
   Conversion: SI to traditional units—Blood glucose: 1mmol/l ≈ 18 mg/100 ml.

Discussion

Our study shows that the postoperative nitrogen balance can be improved by epidural analgesia. Neurogenic blockade for 24 hours after operation is evidently a powerful procedure since its metabolic effects lasted for four days. The patients who had had epidural analgesia were in nitrogen balance from the second day after operation, whereas those who had had general anaesthesia showed a negative nitrogen balance throughout the study, as in other studies.[10] [21] The degree of surgical stress and the intake of energy and nitrogen were similar in both groups, and the difference in nitrogen balance therefore must be related to the epidural analgesia.

The negative nitrogen balance on the day after operation may have been partly due to starvation since all patients received nothing but isotonic saline that day. A normal person who has not undergone surgery excretes 0.35-0.49 mol (5-7 g) nitrogen during the first day of starvation,[22] which is of the same magnitude as in our patients. If the patients had received sufficient calories and nitrogen from the day of operation the negative nitrogen balance might have been abolished in the epidural group.

Epidural analgesia probably affects postoperative nitrogen balance by inhibiting the endocrine stress response, since there was no rise in the blood glucose or cortisol concentration either at operation or afterwards. Epidural analgesia also prevents the increase in plasma cyclic adenosine monophosphate (cAMP)[19] and growth hormone[2] during surgery, but not stress-induced changes in the thyroid hormones.[23] There are no data on plasma catecholamine concentrations during surgery under epidural analgesia, but the fact that this abolishes the plasma cAMP response to surgery suggests that it inhibits catecholamine release. The nitrogen-sparing effect is probably not mediated through an altered insulin : glucagon ratio, since plasma concentrations of these hormones are changed in a similar way during elective surgery under general anaesthesia and under

epidural analgesia.[2] In abolishing the endocrine-metabolic response epidural analgesia also inhibits the postoperative increase in oxygen consumption,[24] thereby reducing the demands on the cardiovascular system.

The increase in plasma glucose and cortisol and the negative nitrogen balance in the control group could not have been caused by halothane, which has a negligible effect on blood glucose[25] and cortisol.[26] Furthermore, it has an inhibitory effect on plasma catecholamines.[27]

Blockade of afferent stimuli from the surgical area is the main mechanism by which epidural analgesia inhibits the endocrine-metabolic stress response,[15] [18] but the concomitant blockade of efferent sympathetic pathways to the liver and adrenal medulla possibly plays an important part as well. The nitrogen-sparing effect of epidural analgesia may not operate in more severe forms of stress, such as burns and sepsis, in which mechanisms other than afferent neurogenic impulses may release the stress response.[15]

The use of epidural analgesia for neurogenic blockade should enable the physiological importance of the endocrine-metabolic response to stress to be clarified. Although Cannon[28] has provided convincing experimental evidence that this stress response is essential for maintaining body homoeostasis, this does not necessarily apply to man. No deleterious effect of the abolished stress response to surgery was found in our study, or when the endocrine-metabolic stress response caused by morphine anaesthesia was inhibited.[29]

Whether other postoperative side effects, such as impaired immunocompetence[30] [31] and phagocytosis,[32] could be prevented by inhibiting the stress response is not yet known. If they could, neurogenic blockade might lower surgical morbidity in high-risk patients.

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SIDE EFFECTS OF DRUGS

Irreversible myxoedema after lithium carbonate

The reported incidence of thyroid hypofunction after long-term lithium carbonate treatment varies from 4%[1] to 12%.[2] Patients receiving such treatment often develop raised serum concentrations of thyroid-stimulating hormone (TSH) and an exaggerated TSH response to TSH-releasing hormone[2] before symptoms of myxoedema appear. Thyroid function is generally thought to return to normal when lithium carbonate is withdrawn. Few cases of irreversible myxoedema after long-term lithium treatment have been reported. One of these patients had raised concentrations of thyroid autoantibodies indicating underlying thyroid disease,[3] and the other apparently recovered one year later.[1]

We describe two patients with no signs of underlying thyroid disease or hereditary predisposition to hypothyroidism who developed irreversible myxoedema after prolonged lithium treatment.

Case reports

Case 1—In April 1973 a 56-year-old man began lithium carbonate treatment for endogenous depression. His symptoms were adequately controlled by treatment, but in August 1974 he presented with gross clinical hypothyroidism without goitre. Serum thyroxine (T4) was 32·2 nmol/l (2·5 µg/100 ml) (normal range 55·3-129 nmol/l (4·3-10 µg/100 ml)), TSH 15·1 mU/l (normal < 1·5), and T3 resin uptake 0·62 (normal 0·80-1·20). He had no known predisposition to thyroid disease and tests for thyroid autoantibodies gave negative results. Lithium treatment was withdrawn and thyroxine sodium 0·15 mg/day begun. TSH returned to normal and subjective improvement was reported. In March 1975 thyroxine sodium dosage was reduced to 0·05 mg/day, but two months later serum TSH was 36 mU/l, T4 47·6 nmol/l (3·7 µg/ml), and T3 resin uptake 0·76, and thyroxine sodium dosage was raised to 0·15 mg/day. One year later thyroxine sodium dosage was again reduced for six months, and thyroid function values fell to below normal.

Case 2—In February 1973 a 54-year-old woman with no evidence of underlying thyroid disease began lithium carbonate treatment for endogenous depression. Lithium treatment was well tolerated until autumn 1974, when she complained of gain in weight (15 kg in six months), intolerance to cold, and tiredness. Serum T4 was 32·2 nmol/l (2·5 µg/100 ml), TSH 48·4 mU/l, and T3 resin uptake 0·90. Goitre was absent. Lithium carbonate was withdrawn and thyroxine sodium 0·15 mg/day instituted. Thyroxine sodium was withdrawn six months later when she was biochemically and clinically euthyroid. After a further six months, however, treatment was reinstituted when she again became clinically hypothyroid. TSH had increased to 50·5 mU/l, T4 was 51·4 nmol/l (4 µg/100 ml), and T3 resin uptake 0·93. Treatment with thyroxine sodium 0·15 mg/day was begun, and she remained euthyroid with normal TSH concentrations for two years.

Comment

Irreversible myxoedema after long-term lithium carbonate treatment may not be as uncommon as previous reports suggest. Other complications of such treatment, including focal fibrosis, tubular atrophy, and glomerulosclerosis,[4] are becoming apparent. A similar